VALUE-BASED DECISION-MAKING OF CIGARETTE AND NON-DRUG REWARDS IN DEPENDENT AND OCCASIONAL CIGARETTE SMOKERS: AN FMRI STUDY

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ABSTRACT

Little is known about the neural functioning that underpins drug valuation and choice in addiction, including nicotine dependence. Following ad libitum smoking, 19 dependent smokers (smoked≥10/day) and 19 occasional smokers (smoked 0.5-5/week), completed a decision-making task. First, participants stated how much they were willing-to-pay for various amounts of cigarettes and shop vouchers. Second, during functional magnetic resonance imaging, participants decided if they wanted to buy these cigarettes and vouchers for a set amount of money. We examined decision-making behaviour and brain activity when deciding to (vs. when not to) purchase cigarettes and vouchers, and 'value signals' where brain activity correlated with cigarette and voucher value. Dependent smokers had a higher willingness-to-pay for cigarettes than occasional smokers and made an irrationally large number of cigarette purchases, while occasional smokers did not. Across both groups, the decision to buy cigarettes was associated with activity in the left paracingulate gyrus, right nucleus accumbens and left amygdala. The decision to buy vouchers correlated with activity in the left superior frontal gyrus, but dependent smokers showed weaker activity in the left posterior cingulate gyrus. Across both groups, within pre-defined ROIs, cigarette value signals were observed in the left striatum and ventromedial prefrontal cortex. Nicotine dependence was associated with greater behavioural valuation of cigarettes and irrational decision-making. When purchasing cigarettes, reward and decision-related brain regions were activated in dependent and occasional smokers; however, dependent smokers displayed weaker activation when purchasing vouchers[FT1]. Moreover, [FT2]for the first time, we identified value signals for cigarettes in the brain.

INTRODUCTION

Addiction can be considered a disorder fundamentally caused by maladaptive decision-making (Redish et al., 2008; Schoenbaum and Shaham, 2008; Ekhtiari et al., 2017). Indeed, decisions to continue to use drugs despite interpersonal or psychological and physical health problems are diagnostic criteria for DSM-5 substance use disorders (American-Psychiatric-Association, 2013). Decisions lie at the heart of our understanding of addiction. However, one critical type of decision that has received scant attention within neuroscientific addiction research is the decision to buy drugs.

Initial behavioural economics research on cigarette purchase (Jacobs and Bickel, 1999; MacKillop et al., 2008) showed that, like for other reinforcers, cigarette consumption (i.e. the number purchased) is at its maximum when cost is at its minimum and decreases as cost increases. Furthermore, measures of demand for cigarettes correlate with nicotine dependence (MacKillop et al., 2008; Murphy et al., 2011; Chase et al., 2013), are sensitive to cigarette cues and withdrawal (MacKillop et al., 2012), and predict future smoking behaviour in those attempting to quit (Mackillop et al., 2015). This demonstrates that addiction to cigarettes can be successfully conceptualised in a behavioural economic framework.

'Neuroeconomics' was born out of the combination of behavioural economics and cognitive neuroscience (Glimcher and Rustichini, 2004; Glimcher et al., 2009), and studies what happens in the brain when economic decisions are made. Building on the existing behavioural economics work, three 'neuroeconomics' studies have examined neural activations associated with decisions to buy drugs. These studies have all combined functional magnetic resonance imaging (fMRI) with a drug purchase task with real, financial consequences (MacKillop et al., 2014; Bedi et al., 2015; Gray et al., 2017).

MacKillop et al. (2014) used the well-validated 'alcohol purchase task' (Murphy and MacKillop, 2006) with 24 heavy alcohol drinkers. The participants made a series of decisions about how many 'mini-drinks' they would buy for a range of prices ($0 to $15). Decisions to buy alcohol were associated with activation in the medial prefrontal cortex (mPFC), posterior parietal cortex (PPC), dorsolateral prefrontal cortex (dlPFC), posterior cingulate cortex (PCC), and left anterior insula. The authors suggest these regions are specifically involved in attention and intentionality (PPC), decisional balance (mPFC and dlPFC) and craving (insula) (MacKillop et al., 2014).

Using an analogous task, the ‘cigarette purchase task’, Gray et al. (2017) examined brain activation when 35 cigarette smokers (who smoked an average of 16 cigarettes per day) made decisions about how many cigarettes they would buy for a range of prices ($0 to $10). Decisions to buy cigarettes were associated with activation of the caudate and deactivation of superior parietal lobule. Elastic decision-making (i.e. when consumption is substantially affected by price) was associated with activation of medial frontal gyrus (meFG), middle frontal gyrus (miFG), inferior frontal gyrus (iFG), insula, anterior cingulate cortex (ACC), parietal lobule and dlPFC. The authors suggest that activity in the caudate was due to its role in goal-directed action, meFG activity related to conflict processing and dlPFC activity associated with inhibitory processes (Gray et al., 2017).

Bedi et al. (2015) used a slightly different approach in which 21 regular cannabis users made yes/no decisions about whether they wanted to purchase a certain number of cannabis puffs (1 to 12) for a specific price ($0.25 to $5). Multivariate analysis was employed to determine which voxels’ activations were associated with decisions to buy cannabis, these were: superior frontal gyrus (sFG), meFG, miFG, PCC, caudate, putamen, insula, inferior parietal lobule and superior parietal lobule. The authors (Bedi et al., 2015) noted similarity in their results to Mackillop et al.’s (2014) results and highlighted activation of bilateral dorsal striatum, which is thought to become more important in directing behaviour as addiction severity increases (Everitt and Robbins, 2005, 2016). Furthermore, they link the insula’s activity with interoception (Naqvi and Bechara, 2009) and the PCC’s activity with subjective value (Clithero and Rangel, 2013).

Much *general* neuroeconomics research has focused on finding neural ‘value signals’ for different commodities, i.e. brain regions where activity is directly proportional to the value of the commodity presented (Montague and Berns, 2002; Plassmann et al., 2007; Rangel et al., 2008; Rushworth and Behrens, 2008; Chib et al., 2009; Bartra et al., 2013). This research has highlighted the critical roles of the ventromedial prefrontal cortex (vmPFC) and ventral striatum (amongst others) in valuation processing. Indeed, in a study which directly informed our methodology (Chib et al., 2009), activity in one region of the vmPFC correlated with subjective value for three different types of reward: food, money and ‘trinkets’ (e.g. a hat). However, drug-related neuroeconomic research has not yet searched for drug value signals. Furthermore, no comparative rewards have been used to investigate brain activity associated with the valuation and purchase of drugs alongside that of non-drug rewards, despite this strategy being employed in other areas of addiction research (Bühler et al., 2010; Chase et al., 2013; Lawn et al., 2015).

Therefore, we do not know: (1) whether nicotine dependence is associated with differential brain activity when purchasing cigarettes, (2) if cigarette value signals exist in the expected brain areas, and (3) how the brain responds when valuing and purchasing cigarettes and non-drug rewards within the same paradigm. In order to address these gaps of knowledge, we conducted a cross-sectional fMRI study comparing dependent and occasional cigarette smokers when they made decisions about purchasing cigarettes and vouchers of varying amounts.

Hypotheses

We hypothesised that dependent smokers would financially value cigarettes more than occasional smokers. Based on the claim that addiction is underpinned by weakened goal-directed drug-seeking (Everitt and Robbins, 2005, 2016), we also predicted dependent smokers would purchase cigarettes in an irrational manner.

We predicted that the decision to purchase cigarettes and vouchers would be associated with activity in reward-related and choice-related regions: mPFC, dlPFC, ACC, PCC, insula, caudate/putamen and mFG/meFG/iFG/sFG. Moreover, we hypothesised that activity in these regions would be greater when purchasing cigarettes and weaker when purchasing vouchers in dependent smokers compared to occasional smokers.

We predicted that activity in the vmPFC and ventral striatum would correlate with subjective cigarette and voucher value, on a trial-by-trial basis. Lastly, based on weaker goal-directed drug-seeking (Everitt and Robbins, 2005, 2016), we predicted that the relationship between subjective value of cigarettes and brain activity would be weaker in dependent smokers than occasional smokers.

MATERIALS AND METHODS

Participants

A cross-sectional study design was employed. Nineteen dependent cigarette smokers (three women) and 19 occasional cigarette smokers (six women) took part[1]. Inclusion criteria for the dependent smokers were: (1) Fagerstrom Test of Nicotine Dependence (FTND) score ≥ 5, (2) smoke ≥10 cigarettes per day on average. Inclusion criteria for the occasional smokers were: (1) FTND=0, (2) smoke 0.5-5 cigarettes per week on average. Inclusion criteria for all participants were: 18-50 years old, right-handed and normal or corrected-to-normal vision with contact lenses. Exclusion criteria were: (1) seeking treatment for a mental health problem; (2) using psychiatric medication; (3) use of any illicit drug once per week or more; (4) quitting smoking; and (5) any MRI contraindications Additionally, occasional smokers were excluded if they had ever been a regular, daily cigarette smoker in the past. Participants were told to smoke as normal before the study (i.e. they were *not* required to abstain from smoking).

Recruitment was conducted via advertisements on Gumtree, in Exeter town centre and in the University of Exeter. Participants were reimbursed £10/hour. All participants were given full information about the study and provided written informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the University of Exeter Ethics Committee.

Assessments

Value-based decision-making task (Chib et al., 2009)

The structure of the task was based on a value-based decision-making task constructed by Chib et al. (Chib et al., 2009). The task was divided into two phases: a pre-scanning auction phase and a scanning choice phase. Both phases involved making purchase decisions about cigarettes and voucher 'bundles', i.e. different amounts of cigarettes/vouchers.

The cigarettes on offer were Marlboro, Camel or Lucky Strike and, within a bundle, they varied in number from one to ten, e.g. '8 Marlboro cigarettes' was one cigarette bundle. In total there

[1] We tested 23 dependent smokers and 20 occasional smokers. We excluded four dependent smokers for the following reasons: one smoked cannabis more than once per week, and we only found out during the testing session; one had a missing structural scan; one had an error in all functional data and one had no willingness to pay data recorded. We excluded one occasional smoker because they had an error in all functional scans. Therefore we had 19 participants in each group.

were 30 cigarette bundles. The vouchers were HMV, Amazon, Waterstones and they varied in amount from one to ten, where one voucher = 20p, e.g. ‘4 Waterstones vouchers’ was one voucher bundle. In total there were 30 voucher bundles. Each phase consisted of 60 purchase decisions.

At the start of the pre-scanning phase, participants were given eight pounds in cash. They were told that, across both phases, one of their choices about cigarette bundles and one of their choices about voucher bundles would be *randomly chosen to happen in reality*. Therefore, they should make every decision like it was real. They could spend a maximum of four pounds on vouchers and four pounds on cigarettes, across both phases.

Pre-scanning auction phase (see figure 1a)

The pre-scanning phase was an auction, in which participants decided how much they would like to spend on the total of 60 different cigarette and voucher bundles, ranging from £0.00 to £4.00. The participant had as long as they wanted for each auction decision. The auction was a Becker-DeGroot-Marschack (BDM) auction (Chib et al., 2009) and a full description can be found in the supplementary materials.

Scanning choice phase (see figure 1b)

Subsequently, the participant entered the scanner and completed the scanning choice phase. The participant faced a series of simple decisions in which they chose whether or not to buy a cigarette or voucher bundle for a set amount of money. The set amount of money (for all trials) was equal to their median willingness-to-pay (WTP) from the pre-scanning auction phase. Each of these choices lasted for three seconds. This three second choice event is the key event for the fMRI analyses in which we investigated value and choice processing across and between the groups. Between the choices there were inter-trial intervals which varied randomly in length from 1 to 10s (with an equal probability for each interval). The 60 trials were fully randomised. The task lasted for nine minutes and 30 seconds. We presented words, rather than images, in the task, in order to reduce cue reactivity.

Other assessments

We also measured depression with the Beck Depression Inventory (Beck et al., 1996), nicotine dependence with the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991;

Fagerström et al., 2012) and the Diagnostic and Statistical Manual 5 (Association, 2013), carbon monoxide using a Bedfont Micro Smokerlyzer (Bedfont Scientific, Harrietsham, UK) and premorbid verbal intelligence with Spot The Word (Baddeley et al., 1993). More details can be found in supplementary materials.

Procedure

Participants attended one two-hour testing session. Before entering the scanner, they completed the questionnaires, blew into the CO monitor and completed the pre-scanning auction phase of the task. Subsequently, they entered the scanner and completed the scanning choice phase of the task, as well as two other tasks, which will be reported elsewhere. After finishing the scanning, one cigarette-related decision and one voucher-related decision from across both phases was selected to happen in reality At the end of the session, the participant was given their bonus payment of cigarettes, vouchers, and remaining money.

Magnetic resonance image acquisition

MRI data were collected on a Philips 1.5T scanner with an 8 channel sense head coil. For functional scans, T2*-weighted, echo-planer images were collected using a sequence with the following parameters: repetition time (TR)=3s, echo time (TE)=50ms. T1-weighted images were collected for the structural scan. Further details can be found in the supplementary materials.

Behavioural data analyses

All behavioural data were analysed using IBM Statistical Package for Social Sciences (IBM SPSS version 21).

Demographics and baseline smoking variables for dependent and occasional smokers are described using means, standard deviations, medians and ranges. They were compared using independent t-tests or Mann-Whitney U-tests, depending on whether the data met requirements for parametric analysis.

ANOVAs with a between-subjects factor of Group (dependent and occasional) and Reward (cigarette and voucher) were employed to analyse behavioural data. Bonferonni corrections were applied to post hoc comparisons. We winsorized any outcome data above or below 2.5 standard deviations from the mean. Further details can be found in supplementary materials.

fMRI data analyses

Data were analysed using SPM12. Movement correction was carried out using 2nd degree b-spline interpolation to realign all functional volumes to the mean functional volume. No participant was excluded for movement, as all participants moved less than twice the voxel size (6mm) in any direction throughout the task. Each person's structural image was co-registered to their mean functional volume. Subsequently, a slice timing correction was carried out on the functional volumes using SPM12's default settings. Then, the co-registered structural image and the functional volumes were spatially normalised into Montreal Neurological Institute (MNI) space using the SPM standard MNI template and affine regularisation. Finally, the functional volumes were smoothed with an isotropic Gaussian kernel for group analysis (8mm full-width at half-maximum).

First level analyses

Functional data were analysed using general linear models. We conducted two main analyses: one concerning BOLD response when a reward was purchased vs. when it was not, and one concerning BOLD response correlated with the subjective valuation of reward.

We modelled the three-second choice events using boxcar functions convolved with the default haemodynamic response function. For the choice-based first-level analyses, the events modelled were: cigarette-choice-purchase, cigarette-choice-don't-purchase, voucher-choice-purchase and voucher-choice-don't-purchase. For each individual we created a cigarette-purchase > cigarette-don't-purchase contrast and a voucher-purchase > voucher-don't-purchase contrast. For the value-based first-level analyses, we modelled all cigarette-choice and voucher-choice events parametrically modulated by the WTP for the reward on offer in that choice. For each participant, we were concerned with the beta associated with the cigarette and voucher parametric modulation term. Movement parameters were also included in all the models, as regressors of no interest.

Second level analysis

Subsequently, second-level random-effects models were used to investigate effects in the entire sample and differences between the dependent and occasional smoker groups. At the second level, we used cluster-based familywise error (FWE) correction to $p<0.05$, with a cluster defining threshold of $p<0.005$. First, across both groups, we investigated cigarette-choice-purchase > cigarette-choice-don't-purchase and voucher-choice-purchase > voucher-choice-don't-purchase using one-sample t-tests. Second, we tested whether dependent smokers had greater cigarette-choice-purchase > cigarette-choice-don't-purchase contrasts, and occasional smokers had greater voucher-choice-purchase > voucher-choice-don't-purchase, using independent t-tests.

Third, we conducted analyses for 'value signals' for cigarettes and vouchers, using one-sample t-tests on the parametric modulation betas from the first-level. We conducted a regions of interest (ROI) analysis using regions based on a meta-analysis of value processing (Bartra et al., 2013): left and right striatum, and the vmPFC (table 1). The regions were defined using MarsBar (http://marsbar.sourceforge.net/) as spheres with co-ordinates in table 1 as the centres, and radii of 5mm. The ROIs were combined into a single mask and included in the second level models. We then extracted the betas using MarsBar for each ROI within each participant. One-sample t-tests were used to investigate value signals across groups and independent t-tests to investigate differences between groups, with Bonferroni corrections. In order to evaluate evidence in favour of the null hypothesis, scaled Jeffreys-Zellner-Siow (JZS) Bayes factors were calculated using an online calculator (http://pcl.missouri.edu/bayesfactor). We used the recommended scaled-information prior of $r = 1$ (Rouder et al., 2009). A cut-off of three is used as evidence in favour of the null and a cut-off of 1/3 is used as evidence in favour of the alternative hypothesis (Rouder et al., 2009). We also conducted a whole-brain analysis for the value signals using the cluster-based correction described above.

We also extracted overall betas from the clusters that showed significant activation for cigarette purchases. Within the dependent smokers, we correlated CO and FTND values with these betas and the value signal betas from the significant pre-specified ROIs. We corrected for the number of correlations; α was reduced to 0.005.

RESULTS

Demographics of participants (table 2)

As a result of our criteria, dependent smokers by definition smoked more cigarettes/day and had a higher FTND. All dependent smokers had at least mild TUD and the majority had severe tobacco use disorder; only three occasional smokers had mild tobacco use disorder.

Behavioural results

Willingness to pay in pre-scanning auction phase

For mean WTP in the pre-scanning auction phase, there was a trend Group by Reward interaction ($F_{1, 36}$=3.874, p=0.057) [Dependent: Cigarette mean (SD): 1.881 (0.589); Voucher mean (SD): 1.618 (0.652); Occasional: Cigarette mean (SD): 1.004 (0.699); Voucher mean (SD): 1.089 (0.673)]. There was also a main effect of Group ($F_{1, 36}$=13.268, p=0.001), whereby dependent smokers had overall higher mean WTP scores than occasional smokers. See supplementary materials for more details.

The groups' overall median WTPs differed significantly as well ($t_{34.323}$=3.853, p<0.001) [Dependent median: mean=1.716, SD=0.556; Occasional median: mean=0.929, SD=0.696).

Number of choices in scanning choice phase (Figure 2a & 2b)

To show that the two phases worked correctly and coherently, we tested the hypothesis that as WTP increased, the proportion of purchases in the scanning choice phase increased. In support of this, we found a significant linear effect of WTP on proportion of purchases (F_{18}=28.705, p<0.001).

For the number of purchases in the scanning phase, there was a Group by Reward interaction ($F_{1, 36}$=5.979, p=0.020), and a main effect of Reward ($F_{1, 36}$=9.005, p=0.005) with cigarettes bought more than vouchers. On exploration of the interaction, the dependent smokers made cigarette purchases significantly more than voucher purchases (t_{18}=3.468, p=0.006), while this was not the case for occasional smokers. Occasional smokers made marginally more voucher purchases than dependent smokers (t_{36}=1.522, p=0.078). There was no evidence of a difference in number of cigarette purchases between the groups.

Dependent smokers made an irrationally large number of cigarette purchases based on their individual WTP values and their set prices (t_{18}=2.973, p=0.032). In other words, the dependent smokers bought cigarette bundles (in the choice phase) for more money than they thought they were worth (in the auction phase). However, this was not the case for vouchers, or for either reward in the occasional smokers.

fMRI Results

Choice-based analysis[2]

Across both groups (table 3 and figures 3 and 4a)

Deciding to purchase a cigarette bundle compared with deciding not to purchase a cigarette bundle was associated with greater activity in three clusters, with peak activations in the (1) left paracingulate gyrus, (2) the left amygdala and (3) the right nucleus accumbens. These clusters extended into (1) the left ventromedial prefrontal cortex and left frontal pole; (2) the right hippocampus, right anterior thalamus and across into the left nucleus accumbens and left anterior thalamus; (3) the left hippocampus and left insular cortex.

Deciding to purchase a voucher bundle compared with deciding not to purchase a voucher bundle was associated with activation in the left superior frontal gyrus, which extended into the right superior frontal gyrus.

Difference between groups (figure 4b)

We tested whether dependent smokers had greater activity while deciding to buy cigarettes vs. deciding not to, compared with occasional smokers. We found no significant activation for this contrast.

We tested whether dependent smokers had weaker activity while deciding to purchase a voucher bundle vs. deciding not to, compared to occasional smokers. We observed a significant cluster of activation in the left PCC, extending into the left precuneus cortex.

Value-based parametric modulation analysis

[2] In these choice-based analyses, two dependent smokers were excluded because they never purchased a single voucher bundle, so the modelling would not work. This left 37 participants (17 dependent smokers and 19 occasional smokers).

Region of interest analysis (figure 6)

Across both groups

We extracted beta values for the parametric modulation term in the left [-6 10 -6] and right striatum [10 12 -6], and ventromedial prefrontal cortex [-2 50 -6]. We then conducted three Bonferroni-corrected one-sample t-tests. For cigarettes, we found significant value signals in the left striatum (t_{37}=2.827, p=0.024) and the vmPFC (t_{37}=3.439, p=0.003). For vouchers, we found no evidence in favour of value signals in these regions.

Difference between groups

We then conducted independent t-tests on the extracted betas for the cigarette parametric modulation terms. We found no significant differences between the groups for the left striatum (t_{36}=0.410, p=0.684), right striatum (t_{36}=1.468, p=0.159) and vmPFC (t_{36}=0.141, p=0.889). A Bayesian analysis provided evidence in favour of there being no group difference in the left striatum (JZS Bayes factor = 3.91) and the ventromedial prefrontal cortex (JZS Bayes factor = 4.17), but not in the right striatum (JZS Bayes factor = 1.67).

Correlations (figure 7)

Within the dependent group, we observed a significant negative correlation between CO and the beta values extracted from the left amygdala cluster in the ‘purchase cigarette bundle > don’t purchase cigarette bundle’ contrast (r=-0.667, p=0.003). No other correlations were significant.

DISCUSSION

We conducted a cross-sectional fMRI study to investigate value-based decision-making of cigarettes and vouchers in dependent and occasional cigarette smokers. In support of our first hypothesis, dependent smokers were more willing to spend greater amounts of money to buy cigarettes than occasional smokers; dependent smokers bought more cigarettes than vouchers; and dependent smokers bought more cigarettes than would be expected 'rationally'. Lending some support to our second hypothesis, across both groups, the decision to purchase cigarettes was associated with significant activation in the left paracingulate gyrus, left amygdala and right nucleus accumbens. The decision to purchase vouchers was associated with significant activation in the left superior frontal gyrus. Dependent smokers activated the left PCC significantly less than occasional smokers when deciding to purchase vouchers, showing a blunted response to non-drug reward purchase. However, opposing our second hypothesis, there were no group differences in neural activity when deciding to purchase cigarettes. Partial support was provided for our third hypothesis: neural value signals for cigarettes were identified in the pre-defined regions of the left striatum and vmPFC, but no group differences, and no value signals for vouchers were identified. We also observed a negative relationship between CO and BOLD response in the left amygdala when purchasing a cigarette bundle, within the dependent smokers.

As predicted, dependent smokers financially valued cigarettes more in the auction phase than occasional smokers. Surprisingly, the dependent smokers were also more willing to spend more money on vouchers than occasional smokers. Previously, we have found no differences in motivation for non-drug rewards between dependent and occasional smokers (Lawn et al., 2015; Lawn et al., 2017). This may be a result of different methodologies: physical effort exertion vs. spending money.

In the choice phase, participants were more likely to buy a cigarette bundle if they had given it a high WTP score in the auction phase. This relationship showed that the participants' behaviour pre-scanning and during scanning was consistent. Furthermore, in the choice phase, dependent smokers chose to buy cigarette bundles more often than voucher bundles, while this was not the case for occasional smokers. This is consistent with previous choice-based research with heavy vs. light cigarette smokers (Hogarth and Chase, 2011, 2012; Chase et al., 2013; Lawn et al., 2015; Lawn et al., 2017).

Notably, dependent smokers chose to buy more cigarette bundles than would be considered rational based on their own individual WTP scores. In other words, even when the cigarette bundle was worth less to them than the price offered, they would still buy it. Behaviourally, this result supports theories of addiction which claim that drug-seeking becomes less goal-directed and more habitual as dependence takes hold (Everitt and Robbins, 2005; Goldstein et al., 2007; Everitt and Robbins, 2016).

Across both groups, buying a cigarette bundle compared with not doing so was associated with activation in three clusters, spanning: (1) left paracingulate gyrus, left ventromedial prefrontal cortex and left frontal pole; (2) left amygdala, left nucleus accumbens, left anterior thalamus, right hippocampus and right anterior thalamus; (3) right nucleus accumbens, left hippocampus and left insular cortex.

Three of these regions were predicted based on the three previous neuroeconomics of drug purchase studies (MacKillop et al., 2014; Bedi et al., 2015; Gray et al., 2017): the anterior cingulate cortex (i.e. paracingulate gyrus), insula and mPFC. The anterior cingulate has long been linked with reward-related decision-making (Bush et al., 2002; Rogers et al., 2004), while the insula is thought to be important in interoception and conscious urges to use drugs (Naqvi and Bechara, 2009). Indeed, cigarette smokers with damage to the insula appeared to have a greater chance of cessation (Naqvi et al., 2007). Our results here further support the role of the insula in maintaining nicotine dependence, via its importance in the decision to buy cigarettes.

Only one previous study (MacKillop et al., 2014) reported mPFC involvement when the drug (alcohol) was bought. Indeed, Bedi et al. (2015) remarked that this area was a notable omission in their neural signature of cannabis purchase. Here we see that the left vmPFC was activated when buying cigarettes, which we expected given its role in tracking value (Plassmann et al., 2007; Chib et al., 2009; Sescousse et al., 2010). We also found activation in the nucleus accumbens during cigarette purchase. The nucleus accumbens is the terminus of the mesolimbic dopamine pathway and is well-known for its part in reward processing (Ikemoto and Panksepp, 1999; Knutson et al., 2001).

In this study, participants smoked *ad libitum* before arriving in order to limit the effect of nicotine withdrawal in dependent smokers, which would not have existed in the occasional smokers, had we enforced an abstinence period. However, the dependent smokers differed in CO levels substantially, demonstrating differences in recent intensity of smoking and therefore varying satiation. Contrastingly, the occasional smokers showed little variation. Given satiation should affect neural processing of cigarette reward (McClernon et al., 2009; Sweitzer et al., 2014), we investigated whether CO was negatively associated with activation in regions involved in purchasing cigarette reward in dependent smokers. This was the case in the left amygdala cluster, which extended into the left nucleus accumbens, right hippocampus and bilateral anterior thalamus. The amygdala is thought to encode the current value of reward (Gottfried et al., 2003) and the striatum is sensitive to valuation changes with smoking satiety (McClernon et al., 2009; Sweitzer et al., 2014) and predicts future smoking (Sweitzer et al., 2016). Future research should test whether nicotine deprivation enhances brain activation when purchasing cigarettes.

Buying a voucher bundle compared with not buying a voucher bundle was associated with activation in the left and right sFG. For their drug purchase contrasts, Bedi et al. (2015) reported activation in the sFG/mFG/meFG; while Gray et al. (2017) reported activation in the mFG/meFG/iFG. We did not observe any frontal gyrus activation for cigarette purchases, but did for voucher purchases. The reason for this is unknown, but the results of all studies combined support a role for the frontal gyrus in reward-related decision-making.

Dependent smokers, relative to occasional smokers, demonstrated weaker activity in the left PCC when purchasing a voucher compared to not. This suggests a weaker neural sensitivity to the prospect of purchasing a non-drug reward in those with nicotine dependence. A weakened brain response to non-drug reward processing has sometimes been observed in cigarette smokers (Peters et al., 2011; Rose et al., 2013); our result extends this putatively diminished brain response to a non-drug reward *decision*.

In our three regions of interest (Bartra et al., 2013), we observed significant associations between individual WTP scores and BOLD response in two of them: the left striatum and the vmPFC. This is the first time that value signals for cigarettes have been identified, and they appear in regions known to be critical in the valuation of both monetary and non-monetary rewards (Bartra et al., 2013). We did not find group differences in these neural value signals, and a Bayesian analysis supported the null hypothesis. This tentatively suggests the relationship between subjective value of cigarettes and brain response is unrelated to nicotine dependence. Surprisingly, we did not find analogous value signals for vouchers, which precludes a discussion of the relationship between nicotine dependence and the brain's sensitivity to non-drug reward value.

Strengths and limitations

This study is highly novel; it is the second study to apply neuroeconomics to cigarette use and the first to investigate the relationship between addiction and neural correlates of drug purchase. Furthermore, it has good ecological validity as an experimental approach as participants actually won real cigarettes and vouchers.

In comparison to the three most relevant previous studies, our sample of 38 is the largest. However, because each group had only 19 participants, type II errors could have occurred due to smaller individual group size. In retrospect, a more natural comparison reward may have been food, as that is a consummatory reward. However, our concern about nicotine's effects on appetite convinced us against that. The inclusion of an abstinence manipulation would presumably enhance differences in neural activity between dependent and occasional smokers (McClernon et al., 2009; Sweitzer et al., 2014) and should be tested in future work.

Summary

In one of the first studies to apply neuroeconomics to cigarette use, we have identified cigarette value signals in the brain for the first time in dependent and occasional smokers. Additionally, we have highlighted the importance of specific brain regions in the purchasing of drug (cigarette) and non-drug (voucher) rewards. Our results suggest that dependent smoking is associated with perturbed behavioural valuation and purchase of cigarettes and vouchers. Further, they provide tentative evidence that dependent smoking is associated with blunted neural activation when purchasing alternative, non-drug rewards, in comparison to non-dependent, occasional cigarette smoking.

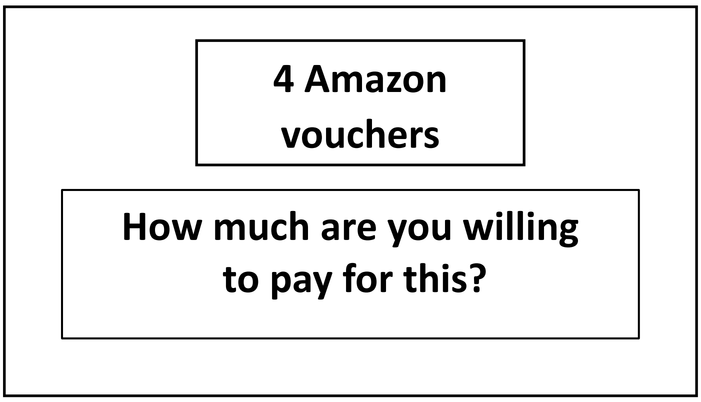
FIGURES

Figure 1.

(a) Example of a pre-scanning auction trial. The participant was asked how much they were willing to pay for a cigarette or voucher bundle (from £0.00 to £4.00). In this example, the bundle is ‘4 Amazon vouchers’. Each voucher was worth 20p, and a cigarette was worth approximately 20p in the UK at the time the study was conducted (2014). This stage of the task provides an individual WTP value for each voucher and cigarette bundle for every participant. The participant could take as long as they wanted for each trial. There were 60 of these trials.

(b) Example of a scanning choice trial. The participant chose whether they would like to buy a cigarette or voucher bundle for a set amount of money, which was equal to their median WTP from the pre-scanning auction phase. If the participant wanted to buy the bundle, in this example 6 Marlboro cigarettes for 70p, they selected the bundle option. If the participant did not want to buy the bundle and did not want to spend any money, they selected the money option. They had 3 seconds to make this choice. Then there was an inter-trial interval for 1-10s. There were 60 of these trials. Across both phases, there were 120 decisions. Two of them were chosen to happen in reality – one cigarette-related decision and one voucher-related decision.

(a)



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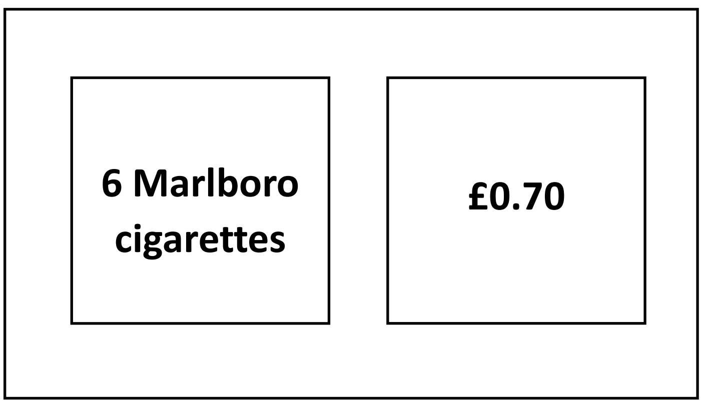
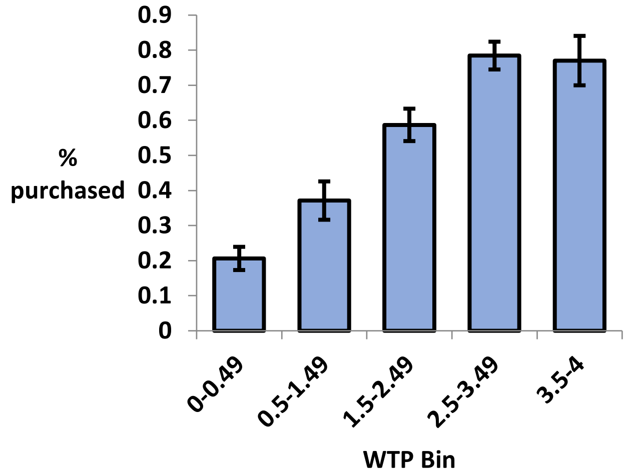


Figure 2

(a) The percentage of the bundles purchased in the scanning choice phase, as a function of the bundles' WTP, across both groups and both rewards (cigarettes and vouchers). Error bars represent standard error

(b) Mean values of number of purchases for cigarette and voucher bundles in the scanning choice phase. There was a significant interaction between Group and Reward (p=0.020), explained by a significant difference between the number of cigarette and voucher purchases in the dependent smokers (p=0.006) but not the occasional smokers. Furthermore, dependent smokers bought an 'irrationally' high number of cigarette bundles based on the individual WTP scores and the price offered (p=0.032). Error bars represent standard error. *p<0.05; **p<0.01.

(a)



(b)

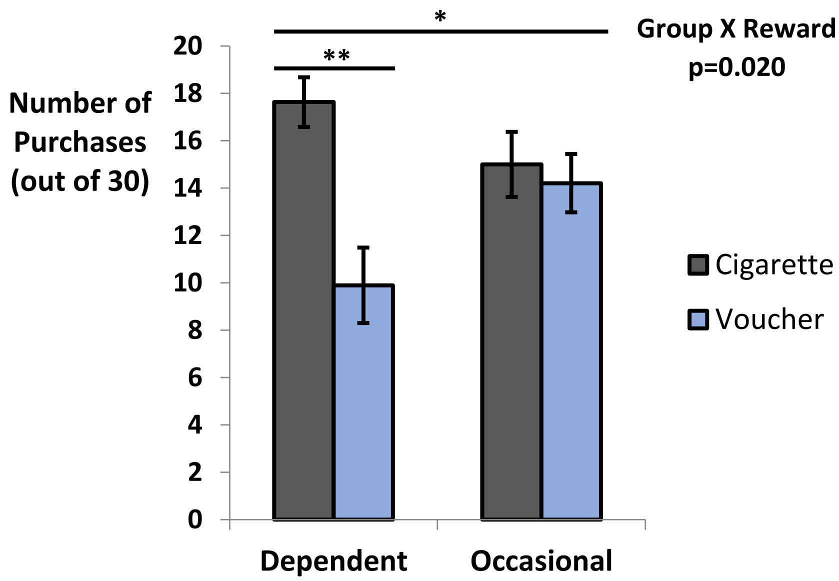


Figure 3

Brain activation when deciding to buy a cigarette bundle vs. deciding not to, across both groups in the vmPFC, left amygdala and right nucleus accumbens. Planes of sagittal views in the following planes: left: x=-3, middle: x=12, right: x=-27. The colours represent z values. The background image is a high-resolution version of the MNI152T1 template.

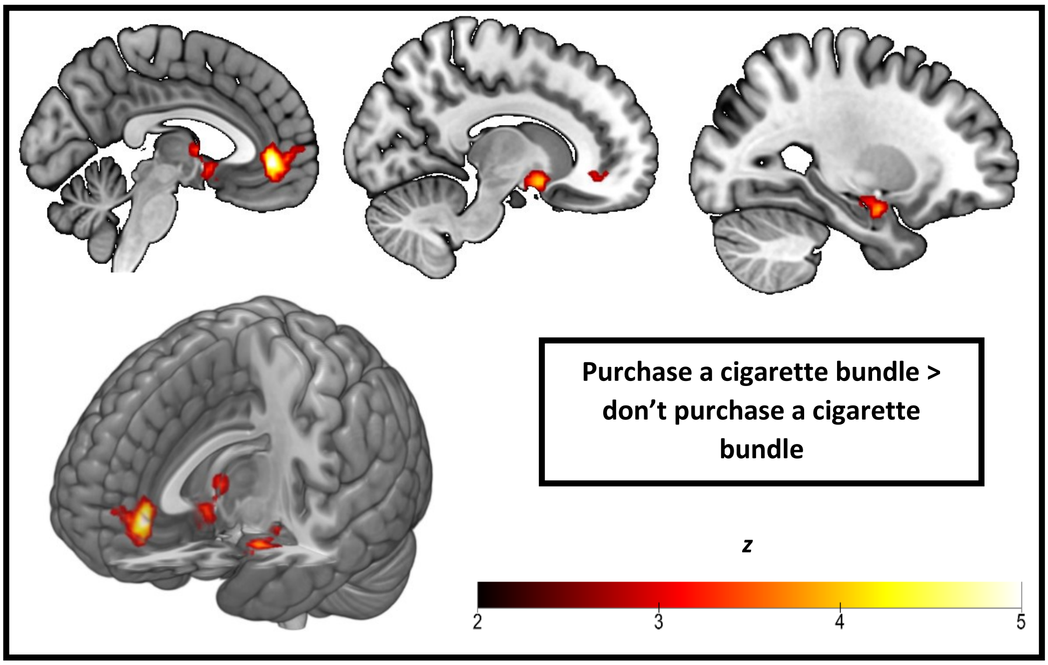
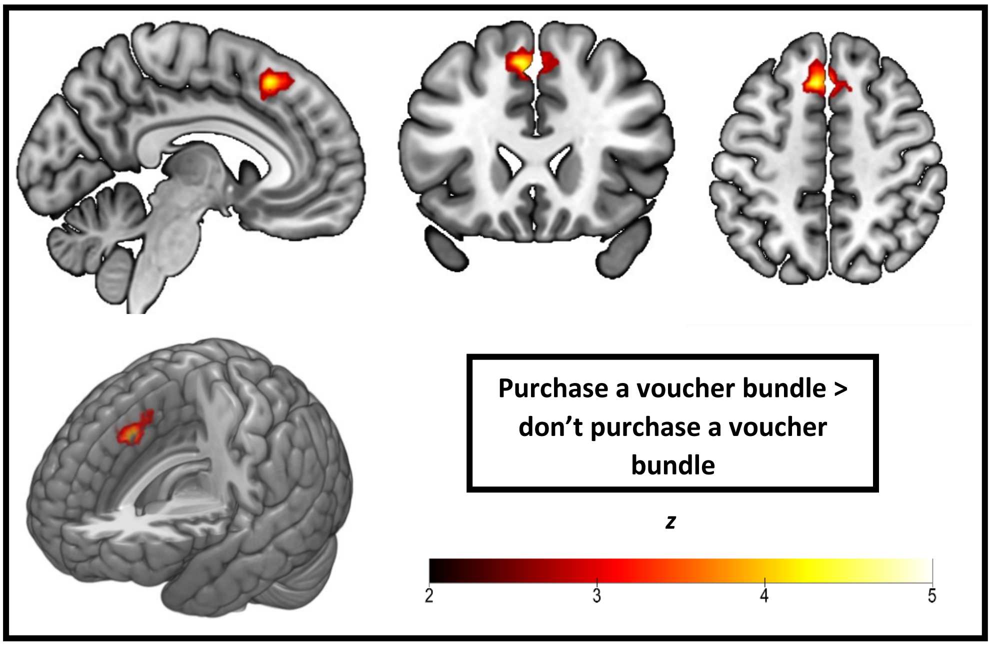


Figure 4

(a) Brain activation in the left superior frontal gyrus when deciding to buy a voucher bundle vs. deciding not to, across both groups. The cluster peak was at [-6 23 50], and the cluster had 108 voxels with p(FWE-corr)=0.014. Sagittal view in plane of x=-6, coronal view in plane of y=23 and axial view in plane of z=50. The background image is a high-resolution version of the MNI152T1 template.

(b) Occasional smokers showed greater activation than dependent smokers for the contrast of deciding to purchase a voucher bundle vs. not, in the left posterior cingulate cortex. The cluster peak was at [-21 -55 32], and the cluster had 86 voxels with p(FWE-corr)=0.041. Sagittal view in plane of x=-9, coronal view in plane of y=-55 and axial view in plane of z=32. The background image is a high-resolution version of the MNI152T1 template.

(a)



(b)

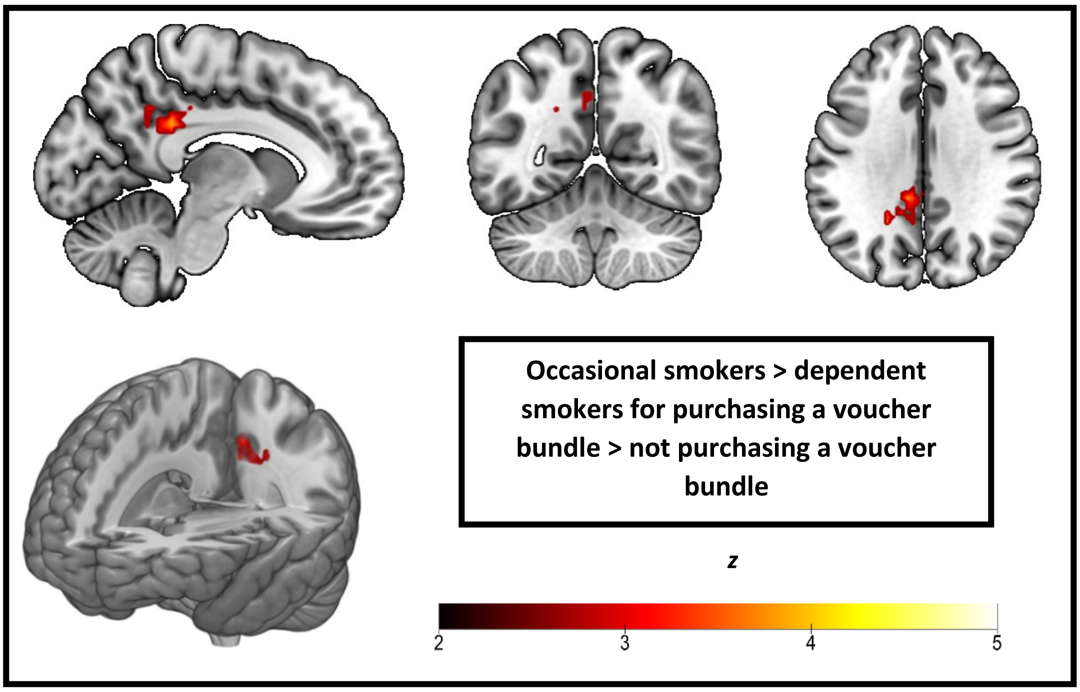

Occasional smokers > dependent smokers for purchasing a voucher bundle > not purchasing a voucher bundle
z
2
3
4
5

Figure 6

(a) Extracted beta values for the parametric modulation term (by WTP) for the three ROIs: left striatum, right striatum and ventromedial prefrontal cortex (vmPFC). Regions were defined with centres from Bartra et al. (Bartra et al., 2013) and radii of 5mm. One-sample t-tests with Bonferroni correction were conducted. Error bars represent standard errors. *p<0.05.

(b) Red spheres show the regions of interest from which the betas were extracted from.

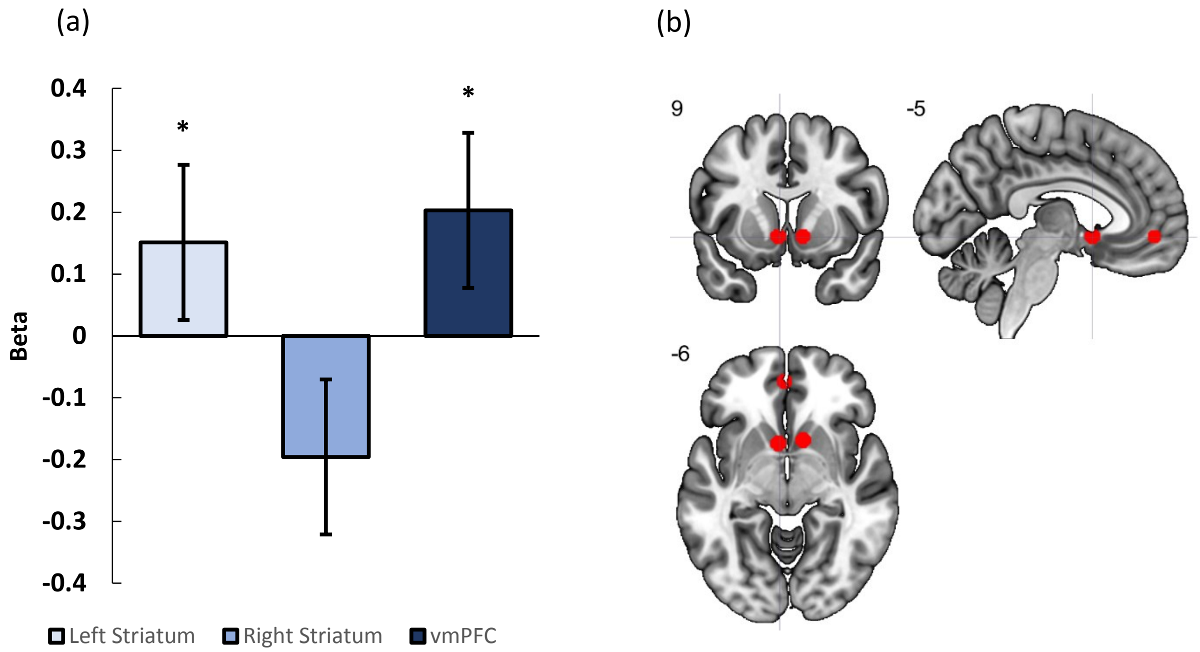
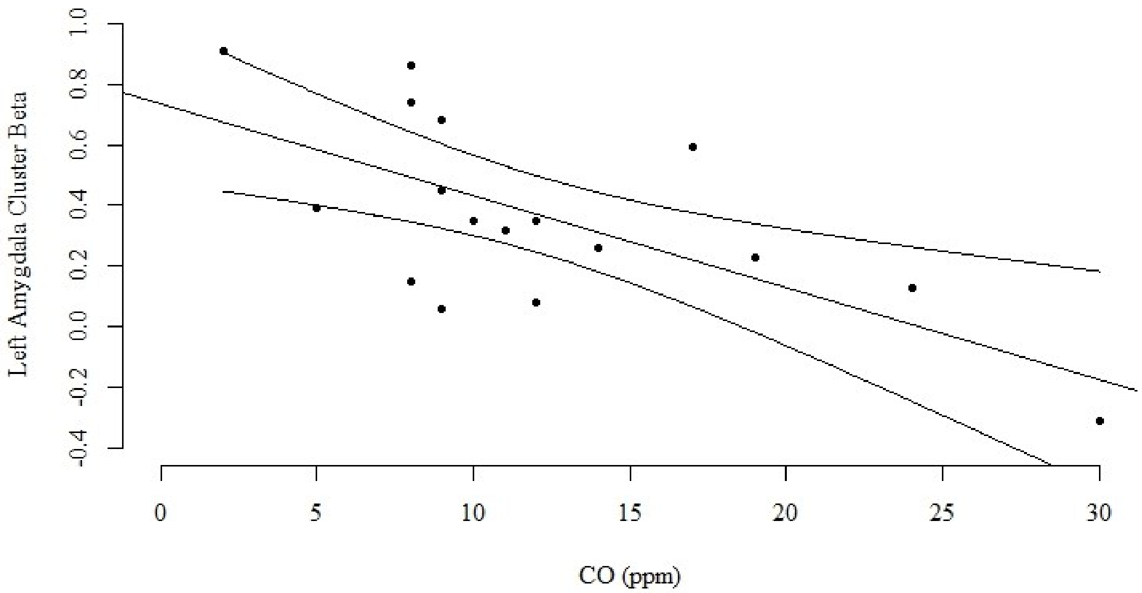


Figure 7

Relationship between expired carbon monoxide (CO) in parts per million (ppm) and overall BOLD response in the significant left amygdala cluster (from the ‘purchase cigarette bundle > don’t purchase cigarette bundle’ contrast), within dependent smokers (r=-0.667, p=0.003). Lines show line of best fit and 95% confidence intervals.



TABLES

Table 1

We used regions from a meta-analysis of value processing (Bartra et al., 2013), which combined monetary and non-monetary rewards: left and right striatum, and the ventromedial prefrontal cortex (vmPFC). We used the centres found in the meta-analysis and used radii of 5mm.

Region	**x**	**y**	**z**
Left striatum	-6	10	-6
Right striatum	10	12	-6
vmPFC	-2	50	-6

Table 2

Demographics of participants. Dependent smokers and occasional smokers did not differ significantly on age, BDI or verbal intelligence, although there were trend differences for age and BDI, with dependent smokers slightly older and more depressed. Occasional smokers had spent significantly more time in formal education than dependent smokers. Dependent smokers smoked more cigarettes/day and had a higher FTND. All dependent smokers had at least mild TUD and the majority had severe tobacco use disorder; only three occasional smokers had mild tobacco use disorder. Mean (SD) [median, range]. FTND = Fagerstrom test for nicotine dependence. Data are not winsorized here. DSM = Diagnostic and statistical manual of mental disorders – 5, tobacco use disorder # symptoms. CO = carbon monoxide. BDI = Beck depression inventory. ***$p<0.001$, $^{o}p<0.1$, ^{np} non-parametric test used, ^{c} divided #cigarettes/week by seven for #cigarettes/day for the occasional smokers.

	Dependent	**Occasional**
Gender (women/men)	3/16	6/13
Age (years) $^{o\ np}$	29.5 (10.7) [24, 18-49]	22.7 (4.4) [21, 19-34]
FTND*** ^{np}	6.2 (1.0) [6, 5-8]	0.0 (0.0)
DSM (none/mild/moderate/severe)	0/4/4/11	9/7/2/1
# cigarettes/day*** ^{c}	18.7 (5.9) [17, 10-30]	0.5 (0.2) [0.6, 0.1-0.8]
CO (ppm)***	12.3 (7.1) [10, 2-30]	2.3 (1.7) [0-6]
BDI^{o}	10.2 (8.7) [9, 0-34]	5.2 [3, 0-17]
Years in education***	12.3 (3.0) [16, 11-20]	16.3 (2.7) [11, 7-19]
Spot the word (# correct)	46.8 (5.6) [48.5, 37-55]	48.7 (6.5) [50, 33-56]

Table 3

Brain activation when deciding to purchase a cigarette bundle vs. deciding not to, across both groups. The table shows: brain regions; cluster-corrected p values for each cluster; k (cluster size) and peaks of each cluster in Montreal Neurological Institute co-ordinates.

Region	***p*(FWE-corr)**	**k**	**Peak co-ordinates in cluster [MNI, mm]**
Left paracingulate gyrus	<0.001	211	-3 44 -4
Right nucleus accumbens	0.001	156	12 5 -13
Left amygdala	0.046	82	-27 -4 -19

Supporting information

Supplementary materials can be found online in the Supporting Information section.

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Authors' contributions

WL, CD, HVC, TF and CJAM designed the study. WL and AB collected the data. WL and LM analysed the data. MBW, CD and JAB assisted with data analysis. WL, LM, CD, JAB, MBW, HVC, TF and CJAM interpreted the results. WL wrote the first draft of the manuscript. WL, TF, CJAM, MBW and JAB provided critical analysis of the manuscript. All authors approved the final version of the manuscript.

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REFERENCES

American-Psychiatric-Association (2013) Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub.

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Baddeley A, Emslie H, Nimmo-Smith I (1993) The Spot-the-Word test: A robust estimate of verbal intelligence based on lexical decision. British Journal of Clinical Psychology 32:55-65.

Bartra O, McGuire JT, Kable JW (2013) The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. Neuroimage 76:412-427.

Beck AT, Steer RA, Brown GK (1996) Beck depression inventory-II. San Antonio 78:490-498.

Bedi G, Lindquist MA, Haney M (2015) An fMRI-based neural signature of decisions to smoke cannabis. Neuropsychopharmacology 40:2657.

Bühler M, Vollstädt-Klein S, Kobiella A, Budde H, Reed LJ, Braus DF, Büchel C, Smolka MN (2010) Nicotine dependence is characterized by disordered reward processing in a network driving motivation. Biological psychiatry 67:745-752.

Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR (2002) Dorsal anterior cingulate cortex: a role in reward-based decision making. Proceedings of the National Academy of Sciences 99:523-528.

Chase HW, MacKillop J, Hogarth L (2013) Isolating behavioural economic indices of demand in relation to nicotine dependence. Psychopharmacology 226:371-380.

Chib VS, Rangel A, Shimojo S, O'Doherty JP (2009) Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. Journal of Neuroscience 29:12315-12320.

Clithero JA, Rangel A (2013) Informatic parcellation of the network involved in the computation of subjective value. Social cognitive and affective neuroscience 9:1289-1302.

Ekhtiari H, Victor TA, Paulus MP (2017) Aberrant decision-making and drug addiction—how strong is the evidence? Current opinion in behavioral sciences 13:25-33.

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nature neuroscience 8:1481.

Everitt BJ, Robbins TW (2016) Drug addiction: updating actions to habits to compulsions ten years on. Annual review of psychology 67:23-50.

Fagerström K, Russ C, Yu C-R, Yunis C, Foulds J (2012) The Fagerström Test for Nicotine Dependence as a predictor of smoking abstinence: a pooled analysis of varenicline clinical trial data. Nicotine & Tobacco Research 14:1467-1473.

Glimcher PW, Rustichini A (2004) Neuroeconomics: the consilience of brain and decision. Science 306:447-452.

Glimcher PW, Camerer CF, Fehr E, Poldrack RA (2009) Introduction: A brief history of neuroeconomics. In: Neuroeconomics, pp 1-12: Elsevier.

Goldstein RZ, Tomasi D, Alia-Klein N, Cottone LA, Zhang L, Telang F, Volkow ND (2007) Subjective sensitivity to monetary gradients is associated with frontolimbic activation to reward in cocaine abusers. Drug and alcohol dependence 87:233-240.

Gottfried JA, O'doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science 301:1104-1107.

Gray JC, Amlung MT, Owens M, Acker J, Brown CL, Brody GH, Sweet LH, MacKillop J (2017) The neuroeconomics of tobacco demand: an initial investigation of the neural correlates of cigarette cost-benefit decision making in male smokers. Scientific Reports 7:41930.

Heatherton TF, Kozlowski LT, Frecker RC, FAGERSTROM KO (1991) The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. British journal of addiction 86:1119-1127.

Hogarth L, Chase HW (2011) Parallel goal-directed and habitual control of human drug-seeking: Implications for dependence vulnerability. Journal of Experimental Psychology: Animal Behavior Processes 37:261.

Hogarth L, Chase HW (2012) Evaluating psychological markers for human nicotine dependence: Tobacco choice, extinction, and Pavlovian-to-instrumental transfer. Experimental and clinical psychopharmacology 20:213.

Ikemoto S, Panksepp J (1999) The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Research Reviews 31:6-41.

Jacobs EA, Bickel WK (1999) Modeling drug consumption in the clinic using simulation procedures: demand for heroin and cigarettes in opioid-dependent outpatients. Experimental and clinical psychopharmacology 7:412.

Knutson B, Adams CM, Fong GW, Hommer D (2001) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. Journal of Neuroscience 21:RC159-RC159.

Lawn W, Freeman T, Hindocha C, Mokrysz C, Das R, Morgan C, Curran H (2015) The effects of nicotine dependence and acute abstinence on the processing of drug and non-drug rewards. Psychopharmacology 232:2503-2517.

Lawn W, Freeman TP, East K, Gaule A, Aston ER, Bloomfield MA, Das RK, Morgan CJ, Curran HV (2017) The acute effects of a dopamine D3 receptor preferring agonist on motivation for cigarettes in dependent and occasional cigarette smokers. Nicotine and Tobacco Research 20:800-809.

MacKillop J, Brown CL, Stojek MK, Murphy CM, Sweet L, Niaura RS (2012) Behavioral economic analysis of withdrawal-and cue-elicited craving for tobacco: an initial investigation. Nicotine & Tobacco Research 14:1426-1434.

MacKillop J, Murphy JG, Ray LA, Eisenberg DT, Lisman SA, Lum JK, Wilson DS (2008) Further validation of a cigarette purchase task for assessing the relative reinforcing efficacy of nicotine in college smokers. Experimental and clinical psychopharmacology 16:57.

Mackillop J, Murphy CM, Martin RA, Stojek M, Tidey JW, Colby SM, Rohsenow DJ (2015) Predictive validity of a cigarette purchase task in a randomized controlled trial of contingent vouchers for smoking in individuals with substance use disorders. Nicotine & Tobacco Research 18:531-537.

MacKillop J, Amlung MT, Acker J, Gray JC, Brown CL, Murphy JG, Ray LA, Sweet LH (2014) The Neuroeconomics of Alcohol Demand: An Initial Investigation of the Neural Correlates of Alcohol Cost–Benefit Decision Making in Heavy Drinking Men. Neuropsychopharmacology 39:1988.

McClernon FJ, Kozink RV, Lutz AM, Rose JE (2009) 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. Psychopharmacology 204:25-35.

Montague PR, Berns GS (2002) Neural economics and the biological substrates of valuation. Neuron 36:265-284.

Murphy JG, MacKillop J (2006) Relative reinforcing efficacy of alcohol among college student drinkers. Experimental and clinical psychopharmacology 14:219.

Murphy JG, MacKillop J, Tidey JW, Brazil LA, Colby SM (2011) Validity of a demand curve measure of nicotine reinforcement with adolescent smokers. Drug and alcohol dependence 113:207-214.

Naqvi NH, Bechara A (2009) The hidden island of addiction: the insula. Trends in neurosciences 32:56-67.

Naqvi NH, Rudrauf D, Damasio H, Bechara A (2007) Damage to the insula disrupts addiction to cigarette smoking. Science 315:531-534.

Peters J, Bromberg U, Schneider S, Brassen S, Menz M, Banaschewski T, Conrod PJ, Flor H, Gallinat J, Garavan H (2011) Lower ventral striatal activation during reward anticipation in adolescent smokers. American Journal of Psychiatry 168:540-549.

Plassmann H, O'Doherty J, Rangel A (2007) Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. Journal of neuroscience 27:9984-9988.

Rangel A, Camerer C, Montague PR (2008) A framework for studying the neurobiology of value-based decision making. Nature reviews neuroscience 9:545.

Redish AD, Jensen S, Johnson A (2008) Addiction as vulnerabilities in the decision process. Behavioral and Brain Sciences 31:461-487.

Rogers RD, Ramnani N, Mackay C, Wilson JL, Jezzard P, Carter CS, Smith SM (2004) Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. Biological psychiatry 55:594-602.

Rose EJ, Ross TJ, Salmeron BJ, Lee M, Shakleya DM, Huestis MA, Stein EA (2013) Acute nicotine differentially impacts anticipatory valence-and magnitude-related striatal activity. Biological psychiatry 73:280-288.

Rouder JN, Speckman PL, Sun D, Morey RD, Iverson G (2009) Bayesian t tests for accepting and rejecting the null hypothesis. Psychonomic bulletin & review 16:225-237.

Rushworth MF, Behrens TE (2008) Choice, uncertainty and value in prefrontal and cingulate cortex. Nature neuroscience 11:389.

Schoenbaum G, Shaham Y (2008) The role of orbitofrontal cortex in drug addiction: a review of preclinical studies. Biological psychiatry 63:256-262.

Sescousse G, Redouté J, Dreher J-C (2010) The architecture of reward value coding in the human orbitofrontal cortex. Journal of neuroscience 30:13095-13104.

Sweitzer MM, Geier CF, Joel DL, McGurrin P, Denlinger RL, Forbes EE, Donny EC (2014) Dissociated effects of anticipating smoking versus monetary reward in the caudate as a function of smoking abstinence. Biological psychiatry 76:681-688.

Sweitzer MM, Geier CF, Denlinger R, Forbes EE, Raiff BR, Dallery J, McClernon F, Donny EC (2016) Blunted striatal response to monetary reward anticipation during smoking abstinence predicts lapse during a contingency-managed quit attempt. Psychopharmacology 233:751-760.